PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CHM-017PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/26052	International filing date *(day/month/year)* 11 August 2004 (11.08.2004)	Priority date *(day/month/year)* 11 August 2003 (11.08.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): G01N 33/00, A01K 67/00, 67/027 and US Cl.: 800/3, 13, 18		
Applicant BRUNSKILL, ERIC W.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 March 2005 (11.03.2005)	13 June 2005 (13.06.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer David Montanari Telephone No. 1-571-272-3108

Form PCT/IPEA/409 (cover sheet)(January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/26052

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))

   ☐ publication of the international application (under Rule 12.4)

   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   ☒ the international application as originally filed/furnished

   ☐ the description:
   pages 1-37 as originally filed/furnished
   pages* NONE received by this Authority on _____
   pages* NONE received by this Authority on _____

   ☐ the claims:
   pages 28-30 as originally filed/furnished
   pages* NONE as amended (together with any statement) under Article 19
   pages* NONE received by this Authority on _____
   pages* NONE received by this Authority on _____

   ☐ the drawings:
   pages 1-18 as originally filed/furnished
   pages* NONE received by this Authority on _____
   pages* NONE received by this Authority on _____

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets/figs _____
   ☐ the sequence listing (*specify*): _____
   ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets/figs _____
   ☐ the sequence listing (*specify*): _____
   ☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/26052

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims NONE	YES
	Claims 1-12	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-12	NO
Industrial Applicability (IA)	Claims 1-12	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-12 meet the criteria set out in PCT Article 33(4), and thus meet the industrial applicability because the subject matter claimed can be made or used in industry.

Claims 1-12 lack an inventive step under PCT Article 33(3) as being obvious over Capecchi (1994) Sci Amer. March 34-41, in view of Brunskill (1999) Mech of Develop. 88: 237-241, Kamnasaran et al (2003) J Med Genet May 40: 325-332, and Lipska et al (2000) Neuropsychopharmacology 23(3): 223-239.

Capecchi teaches transgenic mice comprising a disrupted gene of interest can be used to study the function and establish a phenotype for the desired gene deletion (see pg. 38 figs. 1-2). Capecchi provides methodology for disrupting a gene of interest (see pgs. 38-39 col. 3 parags. 2-7). Capecchi further demonstrates the usefulness of gene targeting as a means to study gene function in the disruption of the HoxA-3 gene, and how disruption of the gene affects limb and organ development in transgenic mice, which aids in determining disrupted gene function (see pgs. 40-41 col. 3 parags. 2-5).

Brunskill et al. teach that neuronal PAS3 (Npas3) is a new member of the helix-loop-helix family of transcription factors, and suggests that Npas3 plays a role in neurogenesis (see pg. 237 col. 2 parag. 1 5-8). Brunskill continues to teach that Npas3 was first dected on whole-mount embryos by in situ hybridization at 9.5 d.p.c. (days after fertilization) in the developing neural tube and continued to incrase in expression through 11.5 d.p.c. and was evident in in the entire neuroepitheilium of the developing central nervous system (CNS) (pg. 238 col. 2 parag. 1). Brunskill continues to teach the primary amino acid sequence of mouse Npas3 (pg. 238 figure 1A) and GenBank accession number for the Npas3 cDNA (AF137871, pg. 241 col. 1 parag. 1 lines 4-5).

Kamnasaran et al. teach that in a mother and daughter affected with schizophrenia a translocation breakpoint junction exists on chromosome 14q 13 between markers D14S730 and D14S70, an interval of 683kb, containing the Npas3 gene (see abstract lines 4-6). Kamnasaran continues to teach that Npas3 gene is proposed to be a susceptibility gene with a contribution to the mental illness associated with schizophrenia observed in the mother and daughter (see pg. 331 col. 2 parag. 2 lines 3-4).

Lipska et al. teaches the importance of animal models in the investigations of the mechanisms underlying a human disease and the design of new treatments (see pg. 223 col. 1 lines 1-3). Lipska continues that most animal models of schizophrenia have focused primarily on phenomena linked to dopamine, because the dopaminergic system has been strongly implicated in schizophrenia (see pg. 224 col. 1 parag. 1 lines 20-24). Lipska continues that existing dopamine models bear no resemblane to schizophrenia, an do not accurately model the disease (see pg. 224 col. 1 parag. 1 bridge col. 2 parag. 2 lines 1-7, and that "it has become increasinly clear that models based on direct manipulations of the dopamine system may have exhausted their heuristic potential and that new strategies need to be developed" (see pg. 224 col. 2 para. 1 last sentence).

Motivation for the claimed mouse is provided by Capecchi teaching that transgenic mice comprising a disrupted gene of interest can be useful in the study of gene function. Motivation is further provided by Brunskill teaching the sequence of the mouse amino acid sequence of Npas3 and the potential role of Npas3 in neurogenesis. Further motivation is provided by Kamnasaran that Npas3 disruption may be a marker for susceptibility to schizophrenia, and motivation provided by Lipska teaching that it is important to have improved animal models to more accurately model schizophrenia.

Thus, it would have been obvious to the ordinary artisan at the time of filing to produce a transgenic mouse whose genome comprises a disruption of the Npas3 gene to determine the role of Npas3 in the development of schizophrenia given the teachings of motivations of Capecchi that disruping a gene of interest is useful for the study of that gene, and in view of Brunskill teaching the Npas3 mouse sequence and it's potential role in neurogenesis, and in further view of the teachings of Kamnasaran that Npas3 gene disruption is linked to an incidence of schizophrenia, and the teachings of Lipska that better models of schizophrenia are needed over the existing dopamine models. There would have been a reasonable expectation of success that a mouse whose gene comprising a disrupted Npas3 gene would be a model of schizophrenia. Thus, the cited prior art provides the requisite teachings, suggestions, and motivation to make and use the claimed genetically modified mouse.